Xe-129 MR Gas Transfer Spectroscopy as a Biomarker for Alveolar Septal Thickening: Reproducibility in Normal Subjects and Idiopathic Pulmonary Fibrosis

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PURPOSE: Idiopathic pulmonary fibrosis (IPF) is characterized by progressive thickening of the interstitial "barrier" between airspaces and capillary red blood cells (RBCs), leading to diffusion impairment whereby the transport of O_2 to the blood becomes the rate limiting factor in gas exchange. Although several therapeutic agents have been suggested, there is no accepted treatment for IPF. Thus, there is an urgent need to develop effective, non-invasive biomarkers to evaluate drug efficacy and assess disease progression. Currently, impaired gas exchange is quantified using DLCO (Diffusing Capacity of the Lung for Carbon Monoxide), but DLCO requires good patient compliance and is highly variable across institutions [1], limiting its use in clinical trials. As an alternative, hyperpolarized (HP) ^{129}Xe MR is uniquely suited to evaluate diffusion impairment due to xenon being highly soluble in blood and tissue. ^{129}Xe displays a large range of chemical shifts in vivo, facilitating the distinction between xenon in the airspaces (0 ppm), dissolved in the barrier tissue (interstitium/blood plasma) (197 ppm) and in RBCs (217 ppm). Because ^{129}Xe reaches the RBCs by first diffusing through the tissue barrier separating RBCs from airspace, we hypothesize that the ratio of RBC/Barrier signal will provide a simple and accurate marker of septal thickening and associated diffusion impairment. Here we quantify the global decrease in RBC uptake in IPF versus control subjects, evaluate inter-subject variability, and begin to establish the degree of reproducibility of this marker for reoccurring scans.

METHODS: HP ^{129}Xe spectra were acquired from 5 healthy volunteers (3 of whom were scanned twice, 4 months apart) and one patient with biopsy-confirmed IPF (scanned twice, 5 months apart) using a GE 1.5T Signa HDx MRI scanner (15.63 kHz BW, TE/TR=0.93/20ms, α=17.20 ± 0.72 º). Subjects inhaled 200 ml of Xe (86% enriched in ^{129}Xe) polarized to 8–15% using a Rb/Xe polarizer (Polarean,Inc, Durham, NC) and diluted with N_2 to a total volume of 1 L. 200 spectra from the whole lung were acquired by exciting dissolved HP ^{129}Xe (gas res. + 3832 Hz) using a 1.2 ms 3-lobe sinc pulse. Spectra were processed in MATLAB (Mathworks, Inc., Natick, MA) using a sliding window of 50 averaged FIDs to obtain 150 pseudo-time resolved frames from the original 200 dissolved-phase spectra. This data was used to define a cutoff beyond which "downstream" RBC signal from the larger vasculature had been effectively crushed. The average signal from frames beyond the cutoff was used to calculate RBC/Barrier ratios and taken to represent dissolved signal arising from the lung's gas exchange regions.

RESULTS & DISCUSSION: Fig 1A shows ^{129}Xe spectra from a control and an IPF subject. The IPF subject shows dramatically reduced ^{129}Xe RBC uptake. This effect is quantified in Fig.1B, showing mean ratios of RBC/Barrier signal in 5 healthy controls vs. the IPF subject. Strikingly, the RBC/Barrier ratio in the IPF subject is 3.75-fold lower than that in control subjects. These results show high reproducibility within a given subject varying only 1.2 % in IPF and on average 5.6% in controls (Fig.1C).The noticeable inter-subject variation in control RBC/Barrier ratio likely results from slow varying physiological factors (e.g. cardiovascular function and subsequent pulmonary perfusion), whereas intra-subject variability may be affected by factors that change daily such as heart rate and hematocrit. RBC/Barrier ratios and DLCO were well correlated (R^2=0.65, Fig 1D), suggesting that ^{129}Xe transfer spectroscopy provides similar information to DLCO, but may yield higher inter-site reproducibility and insights into alveolar-level gas exchange dynamics.

CONCLUSION: We present compelling evidence that global ^{129}Xe spectroscopy of the lungs provides a simple and strong indicator of gas exchange impairment. Results suggest that this technique is highly reproducible over a period of several months. While the inter-subject variability requires further study, it suggests that ^{129}Xe spectroscopy provides additional insight into differences in pulmonary physiology. The origins of these global deviations will serve as grounds for interpreting regional gas exchange assessed by dissolved phase ^{129}Xe MR imaging [2, 3].

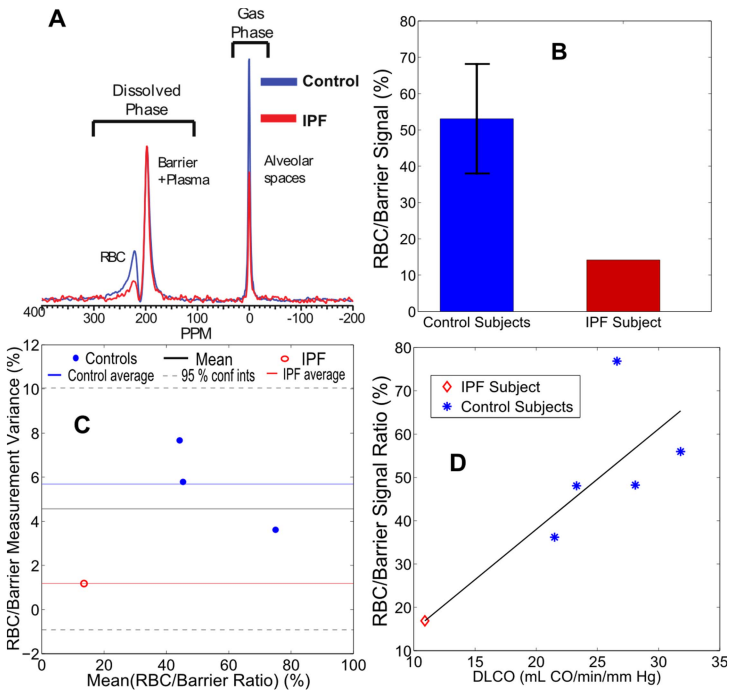

Figure 1: (A) ^{129}Xe spectra; control/IPF overlay. **(B)** Mean RBC/Barrier ratios controls/IPF **(C)** Bland Altman for 3 controls & IPF subject. **(D)** Linear regression plot RBC/Barrier ratios vs. DLCO for 5 controls & IPF subject. R^2 = 0.65.

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